DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 30 1999

Sidney Wolfe, M.D.
Director
Public Citizen Health Research Group
1600 20th Street N.W.
Washington, D.C. 20009-1001

Re: Docket No.92P-0240/CP1

Dear Dr. Wolfe:

This responds to your April 30, 1992, citizen petition regarding nicotine transdermal system products and, secondarily, nicotine chewing gum.[1] Your petition requests that the Food and Drug Administration (FDA) change the labeling for these products to include a prominent boxed warning stating that this product has only been shown to be effective when used as an aid to a comprehensive smoking cessation program and, because it contains nicotine, this product should not be used while the patient is still smoking. For the following reasons, your petition is denied.

The nicotine patch, manufactured by Novartis (Habitrol), SmithKline Beecham (Nicoderm), McNeil Consumer Products (Nicotrol), and Elan (Nicotine Transdermal System (NTS), formerly Prostep), is an adhesive patch worn on the skin that helps smokers quit smoking by continuously releasing nicotine directly into the bloodstream, thus alleviating nicotine withdrawal symptoms. The patch became available in the United States in December 1991, and by 1994 had been prescribed for more than four million Americans.[2]

In July and August 1996, FDA approved new drug applications for Nicoderm and Nicotrol which resulted in a change from prescription to over-the-counter (OTC) status for these systems. In December 1998, FDA approved an NDA for NTS providing for OTC marketing of that system. The other system, Habitrol, remains a prescription drug.

In your petition, you do not challenge the effectiveness of the nicotine patch for smoking cessation, nor do you request a substantial change in the content of the product's labeling. Rather, you request that certain information be moved to the Warnings section and placed in a prominently displayed box. Since issuing its November 1992 interim response to your petition, the Agency has considered available information relating to nicotine substitution

---

[1] Although this petition response, like your petition itself, focuses on the nicotine patch, it also applies to other nicotine substitution products.

[2] In a 1994 meta-analysis of 17 studies of the nicotine patch, investigators found that individuals wearing the active nicotine patch were more than twice as likely to quit smoking as were those wearing a placebo patch, with overall abstinence rates for the active patch of 27 percent at the end of treatment (versus 13 percent for placebo) and 22 percent after 6 months (versus 9 percent for placebo). (Fiore, M. C., et al., "The Effectiveness of the Nicotine Patch for Smoking Cessation," *Journal of the American Medical Association*, Vol. 271, No. 24, p. 1940, June 1994)

92P-0240

PDN1

products, including the views expressed at a July 14, 1992, meeting and an August 1 and 2, 1994, meeting of the Drug Abuse Advisory Committee. Based on available evidence and current regulatory specifications, the requested changes to nicotine patch labeling are not appropriate at this time.

The current FDA-approved labeling for the nicotine patch products, both prescription and OTC, addresses the issues of the comprehensive smoking cessation program and the risks of smoking while using the patch. Current labeling serves the interests of nicotine patch users and physicians. Moreover, with respect to the prescription patch product, the Warnings section is not the appropriate location for the requested statements, and placement of the statements in a boxed warning would constitute a misapplication of an important regulatory tool. Regarding the three OTC patch systems, no provision is made in the regulations governing the labeling of OTC products for the inclusion of boxed warnings, and even if such a warning format were applicable to OTC products, use of a boxed warning would be inappropriate in this case.

I. Prescription Nicotine Transdermal Systems

A. The Warnings section is not an appropriate location for the requested statements.

The Warnings section of the labeling of the prescription nicotine transdermal system states that nicotine can be toxic and addictive, that smoking causes certain diseases and complications, and that the risk of nicotine replacement should be weighed against the hazard of continued smoking while using the patch and the likelihood of achieving smoking cessation without nicotine replacement. The Warnings section does not explicitly state that the patch should be used as part of a behavioral therapy program or that a person should not smoke while using the patch. Instead, as explained below, these cautionary statements are found in other, more appropriate sections of the product labeling.

FDA regulations establish the role of the Warnings section: To describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur (21 CFR 201.57). There is no reasonable evidence, under 21 CFR 201.57, of any serious health hazard associated with nicotine transdermal systems. When used according to the patch's labeling, the drug is a safe and effective aid to smoking cessation.

The approved indication for nicotine transdermal systems is set forth in the Indications and Usage section of the approved prescription product's labeling. In this section, current labeling states that the system is indicated as an aid to smoking cessation and should be used

as part of a comprehensive behavioral smoking-cessation program. This approved indication by no means constitutes a warning, as it makes no reference to potential adverse reactions or safety hazards, and it is therefore properly placed in the Indications and Usage section.

The Individualization of Dosage section of the labeling of the prescription system repeats the message, stating that the success or failure of smoking cessation is influenced by the quality, intensity, and frequency of supportive care, and that patients are more likely to quit smoking if they are seen by physicians frequently and participate in formal smoking-cessation programs. If a patient disregards the labeling and uses the patch without a concomitant behavioral counseling program, the patient may have a decreased chance of achieving cessation, but still the drug poses no serious health hazard.[3]

Labeling of the prescription nicotine transdermal system also contains statements advising against smoking while using the patch. The Precautions section states:

> The patient should be urged to stop smoking completely when initiating [nicotine patch] therapy * * *. Patients should be informed that if they continue to smoke while using [the nicotine patch], they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone.

This caution is appropriately placed in the Precautions section of the patch's labeling. The role of a precaution is to offer information regarding any special care to be exercised by the practitioner for the safe and effective use of a drug, including "information to be given to patients for safe and effective use of the drug, e.g., precautions concerning * * * the concomitant use of other substances that may have harmful additive effects." (21 CFR 201.57(f)(2).)

Any complications resulting from a patient's smoking while using the patch would be attributable to the concomitant use of another substance that may have harmful additive effects. The message not to smoke while using the patch, then, constitutes a precaution and is appropriately placed in this section.[4]

---

[3] The degree to which participation in a concomitant smoking cessation program contributes to success in quiting smoking using the nicotine patch is not entirely clear. In fact, the meta-analysis of 17 patch studies discussed above led investigators to conclude that the patch is effective with minimal adjuvant behavioral counseling. In contrast, there is substantial evidence that nicotine gum is not an effective long-term aid to smoking cessation when not accompanied by substantial adjuvant counseling. (Fiore, M. C., et al., *supra* at 1945)

[4] The admonition to quit smoking upon commencement of patch usage also appears in other sections of the prescription system's labeling. The Dosage and Administration section of the labeling states that "[p]atients must desire to stop smoking and should be instructed to ***stop smoking immediately*** as they begin using [nicotine patch] therapy" (emphasis in original). Likewise, the Individualization of Dosage section of the prescription system's labeling states that

If a patient disregards the labeling and smokes while using the patch, this could, under some circumstances, result in a higher nicotine level in the body than would smoking alone. Although some anecdotal evidence has been offered of a link between smoking while using the patch and such serious adverse effects as myocardial infarction, no such link has been clearly established.[5] Long-term studies would be necessary to provide reliable data about the magnitude of risk from nicotine patch use, particularly given the high risk among smokers generally of such diseases as lung cancer, heart disease, emphysema, and stroke.

The current warnings provided in the prescription system's labeling, together with all of the other cautions in the labeling that specifically address the importance of a behavioral modification program and the dangers of smoking while using the patch, adequately communicate the intended message. There is evidence that many patients do not use the patch in accordance with its labeling; many patients smoke while using the nicotine patch, and many patients do not seek concomitant behavioral modification therapy. However, the Agency knows of no evidence suggesting that patient noncompliance stems from a lack of awareness of the information in the labeling.

B. The potential problems associated with (mis)use of nicotine substitution products do not warrant a boxed warning.

FDA usually requires a boxed warning only where the Agency has "reasonable evidence" of "special problems [associated with a drug], particularly those that may lead to death or serious injury" (21 CFR 201.57(e)). The boxed warning ordinarily is to be based on clinical data, but may sometimes be based on serious animal toxicity (*id.*). Reasonable evidence has not been offered of the nicotine patch's association with a special problem of the type addressed by the regulation on boxed warnings.

The adverse reactions reported in clinical trials of the nicotine patch are described in the Adverse Reactions section of the labeling. In the trials, when reporting adverse events, the investigators did not attempt to identify the cause of the symptom. Concurrent smoking by patients may have contributed to the incidences of some adverse events, the most common of which are a short-lived erythema, pruritus, or burning at the application site. Clinical studies of nicotine patches have shown that the following additional adverse reactions, among others,

---

"[patients] should be instructed to stop smoking completely when the first system is applied."

[5] Because experienced smokers can be quite adept at achieving a desired nicotine level by adjusting their smoking methods, most particularly by altering puff frequency, one cannot assume that a patch-wearer who smokes is necessarily exceeding his or her normal nicotine level, that is, the level achieved as a regular, non-patch-wearing smoker. (See *generally*, 60 FR 41314, 41659-41666, Aug. 11, 1995)

are probably causally related to patch use: Diarrhea, dyspepsia, dizziness, arthralgia, myalgia, abnormal dreams, insomnia, somnolence, nervousness, sweating, skin rash, and abdominal pain.[6]

Again, concurrent smoking may or may not have affected the incidences of these reactions. In any case, none of the reactions reported during clinical studies warrants a boxed warning. These adverse reactions to the patch are not the special problems contemplated by FDA's warnings regulation; rather, they are unexceptional problems, not typically leading to death or serious injury, that are associated with many drugs. Boxed warnings must be reserved to highlight only the most critical information; otherwise, the boxed warning's effectiveness in capturing readers' attention would be substantially diminished, and, as a consequence, crucial information may escape readers' attention in the future. In addition, a boxed warning on these products could mislead consumers into thinking that the patch is associated with special problems, thus possibly deterring smokers' use of the products.

As you note, under 21 CFR 202.1(e)(2)(i), reminder advertisements (including television advertisements) are not permitted for a prescription drug product whose labeling contains a boxed warning related to a serious hazard. Because FDA does not believe such a boxed warning is appropriate for nicotine substitution products, FDA has no objections to advertisements for these products that are not false and misleading and that otherwise comply with relevant regulations. The examples you cite of allegedly misleading advertisements for various brands of nicotine patches all predate the industry's response to FDA's February 1992 letter, to which you refer. FDA believes that advertisements for these products are now in substantial compliance with the regulations.

II. OTC Nicotine Transdermal Systems

As previously stated, in 1996 and in 1998, FDA switched the status of three of the nicotine patch systems, Nicoderm (SmithKline Beecham), Nicotrol (McNeil Consumer Products), and NTS (Elan) from prescription to OTC. Because this switch occurred after you filed your citizen petition, you did not specifically address in the petition whether your concerns extended to the OTC labeling of these products, which, of course, differs from the labeling of the prescription patch products. You did not object to the switch or comment upon it by means of a submission to the docket pertaining to this petition, but when a representative of the Agency contacted you by telephone, in January 1998, you stated that the need for the proposed boxed warning is even more urgent now that some patches are available without prescription. In view of your position that the OTC patch products should also be subject to the boxed warning requirement you propose for prescription nicotine patches, the Agency interprets the requests in your petition to extend to the three OTC patch products, and provides the following response.

---

[6] This list is a consolidation of adverse events reported in clinical studies of all four brands of nicotine transdermal systems. Not all adverse events were observed in all four manufacturers' studies.

Because the three OTC products are no longer subject to the Agency's regulations governing prescription drug labeling, they no longer fall within the purview of 21 CFR 201.57(e), the regulation that provides for the imposition of a boxed warning requirement where, as explained above, a special problem with the drug may lead to death or serious injury. No analogous provision exists for OTC drugs, and FDA has not yet had occasion to consider whether under certain circumstances a boxed warning may be appropriate for OTC drugs.

Nonetheless, even if the Agency were to conclude that OTC drugs, like those available by prescription only, should be subjected to a boxed warning requirement where they present a risk of death or serious injury under certain conditions of use, the OTC nicotine patch products do not present such a risk, and the use of a boxed warning is inappropriate in this context. The reasons underlying this conclusion are very similar to those that support FDA's rejection of your request to place the proposed cautionary statements in a boxed warning in the labeling of the ***prescription*** nicotine patch products. Specifically, the OTC products' current labeling, like the labeling of the two prescription patch products, adequately serves the interests of users by instructing them to cease smoking upon commencement of patch usage, and by stressing the importance of using the patch in conjunction with a comprehensive smoking cessation program.

The labeling of Nicoderm contains no fewer than five references to the necessity of refraining from smoking cigarettes or using other forms of nicotine while using the nicotine patch. The very first entry in the Directions section of the labeling instructs the user to "[s]top smoking completely" when he or she begins using the product, and that message is repeated in other sections of the labeling marked Warnings and How to Use Nicoderm CQ Patches. The labeling bears an additional admonition that states, "DO NOT USE IF YOU Continue to smoke, chew tobacco, use snuff, or use nicotine or other nicotine containing products." Also, in a section marked Some Important Cautions, users are warned that a nicotine overdose may result from the concomitant use of nicotine or nicotine containing products and the patch.

The Nicoderm labeling also repeatedly emphasizes the importance of using the nicotine patch in conjunction with a comprehensive smoking cessation program. In a section entitled To Increase Your Success in Quitting, the labeling instructs users to participate in a support program, as described in a user's guide provided with the patch. That user's guide lists participation in a support program as one of the "keys to success," and further stresses that adherence to a quitting plan enhances one's chances of quitting smoking. Finally, the user's guide also lists the names and toll-free telephone numbers of organizations that can provide further information about support groups for those attempting to quit smoking.

Although less extensive than the labeling of Nicoderm, the labeling of Nicotrol and NTS likewise includes numerous references to the dangers of continued smoking while using the patch, and to the benefits of a comprehensive smoking cessation program. The Directions section of the labeling of both systems begins with an admonition to "[s]top smoking completely" upon commencement of patch usage, and users are instructed to refrain from using the patch if they "[c]ontinue to smoke, chew tobacco, use snuff, or use nicotine gum or

other nicotine containing products." In addition, the Warnings section of the labeling of both systems states that users should not smoke even when not wearing the patch, because nicotine from the patch continues to enter the bloodstream for several hours after the patch is removed.

Regarding participation in a concomitant smoking cessation program, the labeling of Nicotrol and NTS explains that the user's likelihood of success depends in part upon how closely he or she follows a quitting program like the one set forth in a guide (for Nicotrol) and information leaflet (for NTS) provided in the products' packaging. That guide for Nicotrol directs the user to complete and return to the manufacturer a survey concerning his or her smoking habits, which is then used to develop an individualized quitting strategy for the user. Similarly, the user guide for NTS includes a personal stop-smoking guide, in which the user is encouraged to participate in a support group. In addition, the user's guide of both Nicotrol and NTS contains the names and toll-free telephone numbers of organizations that can provide further information about support groups for smoking cessation.

FDA concludes that the warnings and information contained in the labeling of the three OTC nicotine patch products, as summarized above, adequately convey to users the importance of refraining from smoking while using the patch and of participating in a concomitant smoking cessation program. The Agency reiterates that it has not been presented with any evidence suggesting that noncompliance with the two directives at issue in your petition results from users' lack of awareness concerning the information in the products' labeling. Moreover, the Agency notes that the potential drawbacks of implementing a boxed warning requirement -- namely, dilution of the impact of future boxed warnings and creation of a misimpression that the products present a special health problem -- strongly disfavor requiring a boxed warning for the OTC nicotine patch products. Therefore, the Agency rejects your contention that the OTC patch products should be subject to the proposed boxed warning requirement.

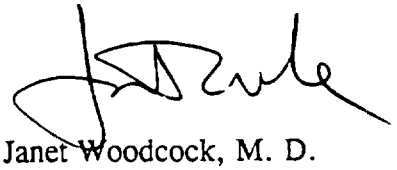
III. Conclusion

Smokers should be provided with every motivation to stop, and those attempting to quit should have access to safe and effective means by which to succeed. As you note in your citizen petition, tobacco use is the single most preventable cause of death and disability in our country, with more than 400,000 people dying each year from tobacco-related illnesses. Despite the massive efforts to educate Americans about the dangers of smoking, nearly 50 million American adults still smoke. The nicotine patch is an effective aid in a motivated smoker's attempt to cease smoking.

Because the risks of nicotine replacement for the vast majority of smokers are acceptable and are substantially outweighed by the risks of continued smoking, nicotine replacement therapy can help to reduce significantly the smoking-related illnesses and deaths in this country. At

this time, available information does not merit a revision of the labeling for nicotine replacement systems. FDA will continue to monitor closely the data relating to these products, including reports of adverse events, and will make suitable changes to the labeling if warranted.

Sincerely yours,



Janet Woodcock, M. D.
Director
Center for Drug Evaluation and Research

cc:
John Slade, M.D.
St. Peter's Medical Center
University of Medicine & Dentistry
of New Jersey, New Brunswick
New Brunswick, NJ 08901